

REMARKS

Claims 29-36 and 45-58 were pending. Claims 30, 32, 34, 36, 45, 48, 52, and 53 were canceled without prejudice. Claims 29, 31, 33, 35, were amended to recite a specific flavivirus, West Nile Virus. Claim 55 was amended to correct a grammatical error. Upon entry of this amendment claims 29, 31, 33, 35, 45-47, 49-51, and 54-58 will be pending.

No new matter has been added

Objections

Claim 55 stands objected for an alleged grammatical error. Claim 55 has been amended to correct the error, rendering the objection moot.

In view of the foregoing, Applicants respectfully request that the objection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 29-36 and 45-58 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Tardei *et al.* (*J. Clin. Micro.*, 38:2232-2239, June 2000) in view of Khromykh *et al.* (*J. Virol.*, 72:5967-5977, July 1998) and Houghton *et al.* (U.S. Patent No. 5,350,671). Applicants respectfully disagree.

The Tardei reference discusses evaluation of immunoglobulin M and IgG enzyme immunoassays in serologic diagnosis of West Nile Virus infection. However, as acknowledged by the Office, Tardei does not mention or even suggest using antibodies against West Nile Virus capsid protein. (Office Action at page 3). Khromykh discusses encapsidation of the flavivirus kunjin replicon RNA by using a complementation system providing kunjin virus structural proteins in *trans*. Khromykh does not make up for the deficiencies in the Tardei reference. Khromykh does not discuss or even suggest the topic of West Nile virus and makes no mention of the capsid protein of the West Nile virus. Houghton discusses HCV (hepatitis C virus) immunoassays employing C domain antigens. But the Houghton references does not cure the deficiencies of the Tardei and the Khromykh references.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation **must** stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and **not** from appellants' disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levingood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would impel one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to combine particular teachings of the cited references and achieve the claimed invention.

According to the Office:

It would have been obvious to incorporate the C protein of a flavivirus, and in particular WNV, into the method of Tardei. One would have been motivated to use the C protein because Houghton discloses methods of immunoassay for detecting antibodies to flavivirus Hepatitis C virus capsid protein. *Houghton says that antigens in the C portion of HCV and other flaviviruses should provide diagnostic reagents* (col. 30, lines 45-54). One would have had a reasonable expectation of success that the C protein or antibodies to C protein would detect exposure because Houghton detects exposure based on the C protein of HCV.

(Office Action at page 3, emphasis in original). However, a person of ordinary skill in the art would not have an expectation of success to use the C protein of WNV or have been motivated to use the WNV C protein based on the Houghton reference as the Office alleges.

Initially, Applicants respectfully disagree with the Office's characterization of the Houghton reference, specifically the characterization of Houghton at col. 30, lines 45-54. The Houghton reference fail to teach or even suggest that the C protein of any virus, other than HCV, can be used as a diagnostic tool or target. Houghton states:

From these predictions it may be possible to identify approximate regions of the HCV polyprotein that could correspond with useful immunological reagents. For example, the *E* and *NS1* proteins of *Flaviviruses* are known to have efficacy as protective vaccines. These regions, as well, as some which are shown to be antigenic *in the HCV isolate* described herein, for example those with putative NS3, C, and NS5, etc. should also provide diagnostic reagents.

(Houghton, col. 30, lines 45-53, emphasis added). The paragraph does not teach or even suggest using the C protein of other flaviviruses in a diagnostic as the Office alleges. Rather, the Houghton reference teaches that the E and NS1 proteins, but not the C protein, of flaviviruses are immunologically important and potentially useful as vaccines. Houghton only refers to using the C protein as a diagnostic for HCV. There is no suggestion in the Houghton reference that suggests using the C protein of other flaviviruses as a diagnostic reagent. Furthermore, Houghton states that there is little similarity between the structural proteins (i.e. C protein) of HCV and other flaviviruses, thereby teaching that only regions that are similar in HCV and other flaviviruses might be used. Houghton states:

Although the non-structural protein region of the putative polyproteins of the HCV isolate described herein and of Flaviviruses appears to be generally similar, *there is less similarity between the putative structural regions which are towards the N-terminus.*

(Houghton, Col. 30, lines 28-32, emphasis added). Thus, the similarities between HCV and other flaviviruses is not throughout the viruses and does not include the structural proteins of the viruses, such as the capsid protein. This is further demonstrated when the amino acid sequences of the capsid proteins of WNV and HCV are aligned. The WNV C protein is only 16% identical

to the C protein of HCV (see attached alignment). Since Houghton teaches only to use proteins such as E and NS1, and not the C protein, the Houghton reference does not teach or motivate one of ordinary skill in the art to use the C protein of other flaviviruses in diagnostics as the Office alleges and there is *no* suggestion or motivation provided by Houghton to use the C protein of WNV as the basis of a method to identify an individual infected with WNV. Rather by discussing the differences between the structural proteins of HCV and other flaviviruses and the emphasis on NS1 and E being useful, one of ordinary skill in the art would conclude that the Houghton reference teaches away from using the structural proteins, such as the capsid protein.

In addition to Houghton teaching away from using the C protein of other flaviviruses, the similarity between the C protein of HCV and the C protein of WNV would not lead a person of ordinary skill in the art to expect that the C protein of WNV would be useful as a diagnostic tool. As discussed above, the WNV C protein is 16% identical to the C protein of HCV and there is no evidence that WNV has similar antigenic regions as those present in HCV C protein. Houghton also teaches that these proteins could be quite different and have different properties. Houghton states:

Thus, while certain domains of the HCV genome may be referred to herein as, for example, NS1, or NS2, it should be borne in mind that these designations are *speculative*; there may be *considerable differences between the HCV family and flaviviruses that have yet to be appreciated*.

(Houghton, Col. 14, lines 13-19, emphasis added). Thus, any designation of an HCV C protein is “speculative” and that according to the Houghton reference, “considerable differences” may exist between the HCV C protein and other flaviviruses C proteins, such as the WNV C protein. Based on the low sequence identity between the HCV C and the WNV C proteins, a person of ordinary skill in the art would believe that *substantial* differences exist between the two proteins. Proteins with a low percentage of similarity would be expected to have different functional properties and different antigenic properties. A person of ordinary skill in the art, therefore, would not assume or expect that a protein from a *different* virus can be used as the basis for a method of identifying an individual infected with the different virus just because a protein in another virus can be used as a diagnostic when the differences in the protein sequences are so

large. Recent scientific evidence also teaches that HCV and WNV are quite different immunologically. Koraka *et al.* (*Microbes and Infection* 4:1209-1215 (2002)) demonstrates that antibodies that recognize one class of flaviviruses (i.e., WNV) do not always recognize HCV (see Koraka *et al.*, Figure 1, p. 1212 and Figure 2, p. 1213). Therefore, a person of ordinary skill in the art would not be motivated to use the C protein of WNV as the basis of a diagnostic assay to identify individuals infected with WNV because there is no expectation of success (little protein similarity and different antigenic properties) and the office has not supplied appropriate motivation to substitute one protein from one virus with a protein from a different virus.

The references also fail to render the present invention obvious because none of the references, either alone or in combination, suggest a method according to claim 29. Claim 29, as amended, recites:

A method of identifying an individual exposed to West Nile Virus comprising the steps of:

- a) contacting antibodies for West Nile Virus capsid protein with a sample from the individual; and
- b) detecting whether said antibodies are bound to West Nile Virus capsid protein from the sample,

wherein detection of binding of the antibodies to West Nile Virus capsid protein is indicative of exposure of the individual to West Nile Virus.

The method discussed in Tardei is the opposite of what is presently claimed in claim 29. In Tardei, serum containing antibodies to West Nile Virus is taken from individuals and tested against whole cell lysates from cells that have been infected with WNV to determine if an individual had been infected with West Nile Virus, but the Tardei method can make no determination as to whether the virus is still present in that individual. In claim 29, antibodies are tested against a sample taken from an individual that contain proteins determine if the West Nile Virus capsid protein is present. Thus, using the method of claim 29, one of ordinary skill in the art can also determine if an individual has the virus or a viral component in their sample, something that cannot be done using the methods described in the Tardei reference, which only detects the immune response by the individual not the actual virus or viral component. There is

no suggestion in Tardei to look for the West Nile Virus capsid protein no matter the method used and there is no suggestion or motivation to look for WNV C protein in a sample taken from an individual using antibodies. Additionally, there is no motivating force in the references alone or in combination to produce the method of claim 29.

The general motivations identified in the Office Action **are not** a “motivating force” that would “impel” persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention. Such statements, at most, raise an inappropriate “obvious to try” standard. Indeed, the court made it clear that it is improper to reject claims as “obvious to try” where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, “focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.” *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

In addition, it appears that the only motivation that the Office is using to combine the references is the use of the Applicants’ specification and hindsight reconstruction, which is strictly forbidden. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) (“One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”). When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [**10] elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . .

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and *with no knowledge of the claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed . . .

To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharm, Inc., 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2D 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis supplied). It appears that the Office has done what Yamanouchi reaffirms should not be done -- used Applicants' specification as a blueprint.

In addition to the Office's requirement of providing a specific motivation to combine the references, which the Office has not provided, the Office must also demonstrate that the references, when combined, yield the claimed invention. However, the references when combined do not yield the claimed invention and therefore cannot render the claims obvious. None of the references either alone or in combination recite all the elements of the pending claims. The combination of the references do not contain all the elements of the claim so that upon combination a person of ordinary skill in the art yield the claimed invention. The references do not disclose 1) contacting antibodies for West Nile Virus capsid protein with a

sample from an individual; 2) detecting whether the antibodies are bound to West Nile Virus capsid protein from the sample; and 3) wherein the detection of binding of the antibodies to West Nile Virus capsid protein is indicative of exposure of the individual to West Nile Virus as is claimed in claim 29. The combination of the references either alone or in combination also do not recite all the elements of the other pending claims as well.

None of the references refer to the capsid protein of West Nile Virus to identify an individual exposed to West Nile virus. The Houghton reference refers to the similarity of HCV and West Nile only in the non-structural proteins and the similarities are limited to the hydrophobicity of the proteins, there is no mention of sequence similarity (see, Houghton, column 108, line 66 – column 109, line 20). Furthermore, the references do not suggest detecting whether antibodies are bound to the West Nile Virus capsid protein. Therefore, either alone or in combination the references do not produce the claimed invention.

Thus, in view of the foregoing, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

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V. Conclusion

The claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned representative at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,



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Attachments: Sequence alignment of West Nile Virus Capsid protein and HCV capsid protein
Koraka *et al. Microbes and Infection* 4:1209-1215 (2002)